Pergamon

Tetrahedron Vol. 50, No. 6, pp. 1651-1664, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $6.00+0.00

0040-4020(93)E0066-O

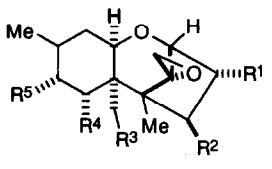
Enantioselective Synthesis of an *Ent*-Trichothecene[1]

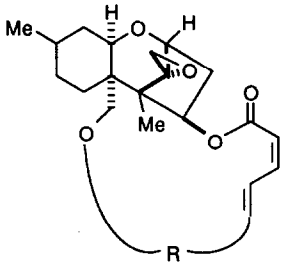
John C. Gilbert* and Robert D. Selliah
Department of Chemistry and Biochemistry, The University of Texas at Austin
Austin, Texas 78712

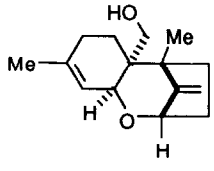
ABSTRACT: A convergent route for the enantioselective synthesis of trichothecenes is described. A key step in the synthetic sequence is an Ireland-Claisen rearrangement that occurs with total facial selectivity and high diastereoselectivity. The *relative* stereochemistry about the vicinal quaternary centers of the major diastereomer is that of the trichothecene skeleton, but the *absolute* stereochemistry is opposite to that of the natural products.

INTRODUCTION

Trichothecenes, a class of sesquiterpenes of fungal origin, show diverse biological activity ranging from high toxicity to humans and farm animals to antiviral, insecticidal and antitumor properties.[2] The most toxic metabolites are T-2 toxin (**1a**) and 3-acetyldeoxynivalenol (**1b**),[3] and feed refusal, decreased performance and emesis in farm animals have been attributed to them.[4] On the beneficial side, anguidine (**1c**) and verrucarin A (**2**) have been found to be highly active antitumor agents.[5] For example, **1c** progressed to Phase II clinical trials against advanced breast cancer but was dropped from further testing due to its acute toxicity;[6] it is believed that anguidine could serve as an antitumor agent if compounds were found that could protect normal tissues against its toxicity, however.[7]

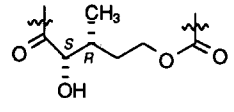






1a R^1 = OH, R^2 = R^3 = OAc, R^4 = H, R^5 = $OC(O)CH_2CHMe_2$
1b R^1–R^4 = OH, R^5 = H
1c R^1 = OH, R^2 = R^3 = OAc, R^4 = R^5 = H

R =



2

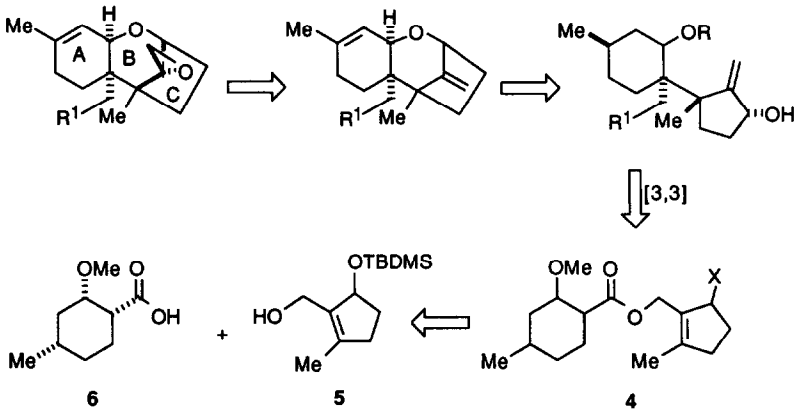
(+)-(**3**)

Continuing interest in the biological activity of trichothecenes therefore provides impetus for the development of efficient routes for the preparation of these compounds in enantiomerically pure form. Despite the number of papers in which the synthesis of trichothecenes as racemates is described,[8] we are aware of only two reports involving the formation of these compounds in optically active form.[9] In this connection, we recently communicated an efficient and highly convergent enantioselective route for the preparation of (+)-15-hydroxytrichothec-9,12-diene (**3**)[10] and the present report provides the details of that effort.

RESULTS AND DISCUSSION

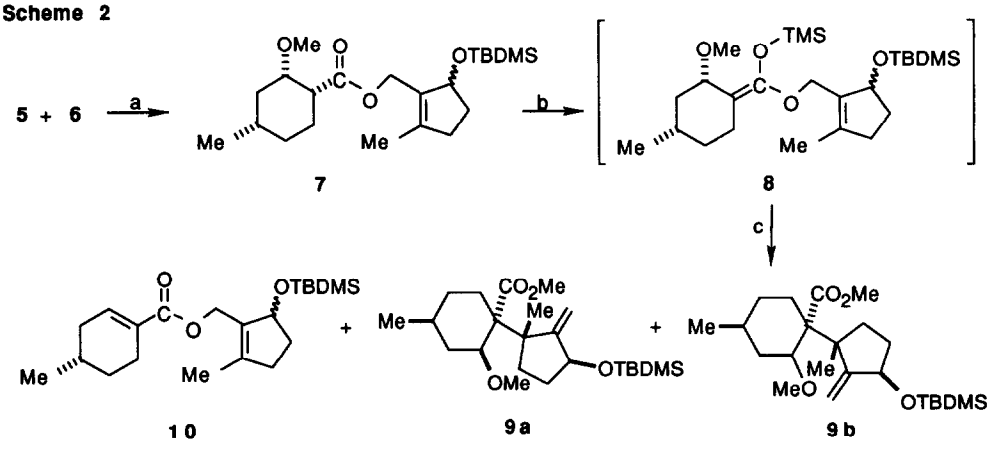
The overall synthetic strategy is portrayed in Scheme 1. The plan was to construct the key bond connecting the vicinal quaternary centers via an Ireland-Claisen rearrangement[11] of the allyl ester **4**. It was anticipated that this compound could be prepared from the known allylic alcohol **5**[12,13] and the β-methoxycarboxylic acid **6**, previously used in the synthesis of optically active trichodiene.[10,14a] The sequence was to be completed by formation of the B-ring via a Group 3 biomimetic cyclization.[15]

Scheme 1



Esterifying acid **6** (45% ee)[10,14a] with racemic **5** according to the method of Turner *et al.*[16] afforded esters **7** (Scheme 2). Analysis by ^{1}H NMR spectroscopy revealed the product to be an equimolar mixture of the

Scheme 2

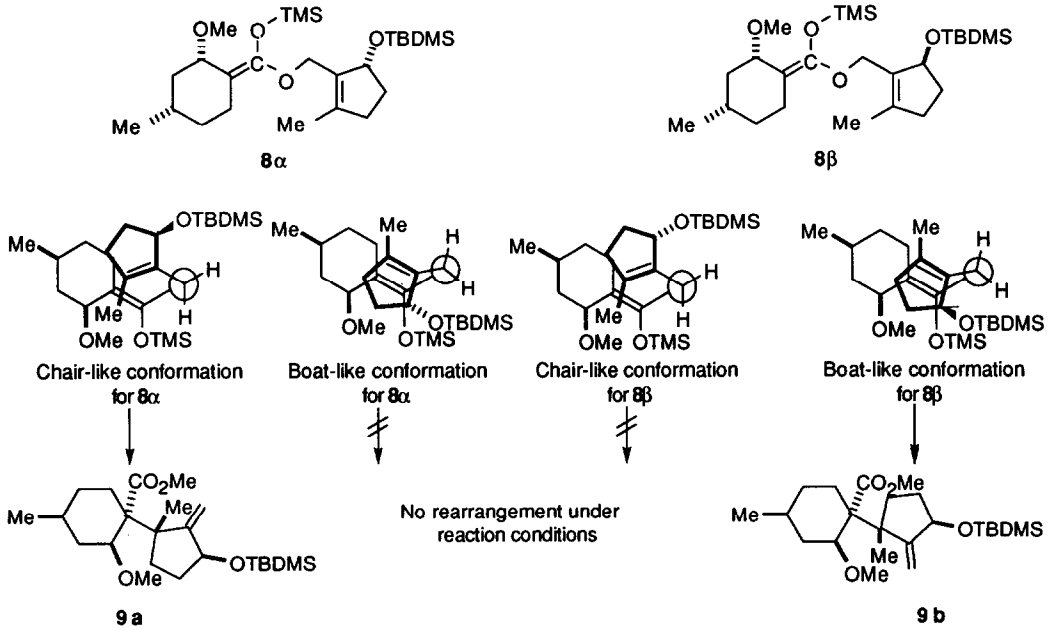


Reagents: a. MsCl, TEA, CH_2Cl_2, DMAP, 77%; b. LDA, TMSCl, TEA, THF, -110 °C; c. (*i*) reflux, (*ii*) dil. HCl, (*iii*) CH_2N_2/ether; 45% (combined yield).

two possible diastereomers, which were inseparable by chromatographic methods. The crucial Ireland-Claisen rearrangement was effected on this mixture by adding a precooled solution of the esters in THF to a solution of LDA, TMSCl, and triethylamine (TEA) held at -110 °C, followed by heating under reflux;[11b] such conditions held formation of **10** via a β-elimination pathway to 4-5%. Following hydrolytic work-up, esterifying the reaction mixture yielded two diastereomeric esters in the ratio of 92:8, as shown by ^{1}H NMR analysis.

Preferential formation of the *Z*-ketene silyl acetals **8** is presumed on the expectation of chelation control in forming the ester enolate, as precedented in our earlier approaches to trichodiene.[14] The silyl acetals **8** are presumably formed in an equimolar amount, and their rearrangement could potentially afford eight diastereomers, based on the possible combinations of chair and boat conformations and *re* and *si* facial attack (Scheme 3). However, our observations of the facial selectivity for a closely analogous rearrangement in the synthesis of trichodiene[14a] suggested that the isomerization should occur from the *re* face of ketene silyl acetal **8**, and such an event reduces the number of possibilities to four, as seen in Scheme 3. Considering the various conformations illustrated in this scheme leads to the conclusion that **9a** and **9b** should correspond to the products obtained, with the former diastereomer predominating.

Scheme 3

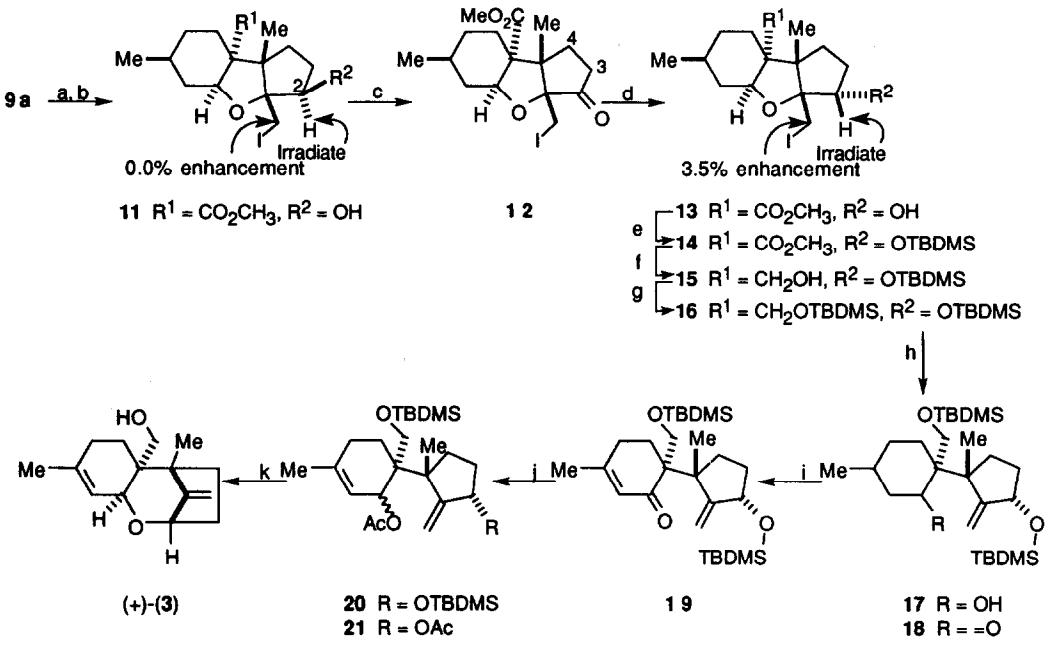


The rationale for this result is developed as follows. There is a known preference for the chair-like conformation in the Ireland-Claisen rearrangement of substrates analogous to ketene silyl acetal **8**[14,17]. Indeed, a substrate *identical* to **8** with the exception that it lacks the OTBDMS moiety on the cyclopentyl ring favors just such a conformation.[14a] The OTBDMS substituent is not a factor in defining the energy of the chair-like conformation of **8α**, but it is expected to destabilize the corresponding conformation of **8β**. Similarly, this

group should significantly destabilize the boat-like conformation of 8α but not that of 8β. Hence the major isomer, assigned as **9a**, arises from isomerization through a chair-like geometry of the ketene acetal 8α, whereas the minor isomer **9b** results from the boat-like rearrangement of the diastereomer 8β. Consistent with this analysis is the observed 92:8 ratio of the two products, which corresponds to the chair-boat selectivity observed in related systems.[14] In summary, it is not surprising that isomerizing an equimolar mixture of 8α and 8β would effect a kinetic stereoselection to afford only two diastereomers, with **9a** predominating.

Based on this analysis, **9a** should have the same relative stereochemical disposition about the vicinal quaternary centers as the trichothecenes. This was confirmed by conversion of **9a** into (+)-**3** by way of the chemical transformations outlined in Scheme 4. The mixture of esters **9** was desilylated with tetra-*n*-butylammonium fluoride (TBAF), and the resulting hydroxyesters were treated with $I_2/NaHCO_3$ to afford the

Scheme 4



Reagents: a. TBAF, THF, 82%; b. I_2, $NaHCO_3$, CH_3CN, 0 °C, 87%; c. Swern ox., 98%; d. $NaBH_4$, CH_3OH, 99%; e. TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 99%; f. DIBAL-H, toluene, 83%; g. 2,6-lutidine, TBDMSOTf, CH_2Cl_2, 99%; h.*(i)* Zn, pyridine, 95% EtOH, THF, reflux; *(ii)* Swern oxidation, 70% (two steps); i. *(i)* LDA, THF, -78 °C, PhSeBr; *(ii)* H_2O_2, pyridine, CH_2Cl_2, 85%; j. *(i)* DIBAL-H, toluene, 0 °C; *(ii)* Ac_2O, pyridine, anhy. K_2CO_3, 35% of **20** and 31% of **21** (two steps); k. **20**, HF·pyridine (excess), 0 °C to rt, CH_3CN, 85%.

single iodocyclization product **11**. The fate of the minor isomer under the iodocyclization conditions is not known because the corresponding iodocyclization product was not isolated. Based on the expected *re* facial selectivity for the rearrangement (*vide supra*), the configuration of the hydroxy group at C-2 (trichothecene

numbering) in **11** is not that required for the final biomimetic cyclization, so the configuration at this center had to be inverted. This was accomplished in two steps via an oxidation/reduction sequence. Thus, Swern oxidation[18] of **11** provided the ketoester **12**, which was then reduced with $NaBH_4$ to give the hydroxyester **13**.[19] Proof that net inversion of configuration at C-2 had been effected by this sequence came from difference nuclear Overhauser experiments with **11** and **13**. Irradiating C(2)-H in **11** caused no enhancement in the resonance for the iodomethylene group, whereas corresponding irradiation of C(2)-H of **13** provided a 3.5% enhancement in the signal for one of the protons of this methylene group (see Scheme 4). This confirms that the hydroxy and the iodomethylene groups are cis in **11** but trans in **13**.

With establishment of the required configuration at C-2, the hydroxyl group in **13** was then converted to the TBDMS ether **14**. Reducing the ester function of **14** with DIBAL-H, followed by protection of the resulting alcohol **15**, afforded the bis-OTBDMS product **16**. The iodoether **16** was initially subjected to reductive cleavage with Zn in aqueous ethanol, but these conditions led to complete desilylation at C-2. However, using a solvent system comprised of THF, pyridine and 95% ethanol afforded the desired product **17**. It is likely that Zn^{2+} formed at the site proximal to the C-2 silyl ether fosters the deprotection; sequestering zinc ion with added pyridine[20] successfully suppresses this undesired process. Crude **17** was immediately oxidized under Swern conditions[18] to afford **18**. Applying the method of Reich *et al.*[21] to **18** produced the enone **19**, which contains the necessary functionality and carbon skeleton for conversion into a trichothecene.

To accomplish this, the enone was reduced with DIBAL-H, and the crude reduction product was immediately acetylated with the expectation of obtaining a single allyl acetate **20**. Surprisingly, a nearly equivalent amount of the diacetate **21** was also formed. Desilylation at C-2 was apparently occurring,[22] most likely during the reduction with DIBAL-H. Unfortunately, the limited supply of enone **19** available at this stage of the synthesis precluded optimization of this transformation. Nonetheless, it is reasonable to expect that using a more bulky silyl protecting group to protect the C-2 hydroxy group would suppress this undesirable side reaction.

With the allyl acetate **20** in hand the stage was set for the construction of the B-ring of trichothecene by way of a biomimetic cyclization. Thus, treating a solution of **20** in acetonitrile with an excess of HF·pyridine afforded **3** in 85% yield. Critical for assigning the trichothecene skeleton to **3** were ^1H NMR chemical shifts—determined by 2D-NMR methods—and the coupling constants of the protons at C-2 (4.27 ppm, J = 4.9 Hz) and C-11 (3.68 ppm, J = 5.4 Hz), as well as the ^{13}C NMR chemical shifts. These data correlate precisely with those expected for the carbon skeleton of a trichothecene.[24] Deoxytrichothecene **3**[25] is dextrorotatory and should be of 45 ± 2% ee, based on the known ee of **6** and the expected complete facial selectivity of the [3,3]-sigmatropic rearrangement.[14] The *re* facial selectivity of the rearrangement allows the prediction that (+)-**3** has the absolute configuration of the unnatural antipode as shown. The natural trichothecenes can thus be prepared from the enantiomer of **6**, which is obtainable in two steps from the β-hydroxyester derived from chemical reduction of the known ethyl (4*R*)-4-methyl-2-oxocyclohexanecarboxylate.[26]

In summary, (+)-15-hydroxytrichothec-9,12-diene (**3**) was prepared in 3% overall yield from the β-methoxyacid **6**. The synthetic route leading to **3** has considerable further potential derived from further functionalization of ketone **12** at C-3 and C-4 (see Scheme 4), which would provide access to more highly oxygenated trichothecenes such as calonectrin (**1d**) and anguidine (**1c**). Furthermore, we believe that novel

analogs of trichothecenes of possible therapeutic value are preparable by this method. Work in our laboratory is presently focused on exploring such possibilities.

EXPERIMENTAL SECTION

Chromatography of product mixtures was effected by flash column chromatography over silica gel, according to the procedure described by Still, *et al.*[27] Optical rotations were measured on solutions in $CHCl_3$ using a Perkin-Elmer 141 Polarimeter. Chloroform was passed through a short pad of activated basic alumina prior to use.

All anhydrous reactions were performed under an inert atmosphere of dry N_2 or Ar. All reaction vessels, syringes and hypodermic needles used in these reactions were dried in an oven at 120 °C for at least 12 h and cooled under an atmosphere of N_2 or in a desiccator. Solvents were dried by distillation, under an atmosphere of N_2, using the drying agents sodium benzophenone ketyl for tetrahydrofuran (THF), and CaH_2 for dichloromethane (CH_2Cl_2), triethylamine (TEA), diisopropylamine, and dimethylsulfoxide (DMSO); THF and CH_2Cl_2 were used immediately after distillation, whereas the other solvents were stored over 4 Å molecular sieves. Skelly-B was stirred over conc. sulfuric acid for at least 24 h, then over sodium carbonate for 24 h, after which it was filtered and distilled. All other reagents and solvents were purified, as necessary, according to standard procedures.[28] Alkyllithiums were titrated by the method of Suffert.[29] Solutions were concentrated by rotary evaporation at water aspirator pressures.

Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on samples in $CDCl_3$, using General Electric spectrometers operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, unless specified otherwise. Chemical shifts (δ) are reported in ppm from tetramethylsilane. All title compounds were judged to be >95% pure by ^1H NMR spectroscopy. Infrared spectra (IR) were recorded on thin films unless noted otherwise, using a Beckman Acculab-8 spectrophotometer or on a Nicolet 510P FT-IR instrument.

{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy](3-methyl-2-cyclopentenyl)-2-methyl} (1*R*,2*S*,4*S*)-2-Methoxy-4-methylcyclohexanecarboxylate and {(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy](3-methyl-2-cyclopentenyl)-2-methyl} (1*R*,2*S*,4*S*)-2-Methoxy-4-methylcyclohexanecarboxylate (7).

A solution of acid **6** (8.0 mmol) in 15 mL of CH_2Cl_2 was placed in a dry 25-mL flask, under an Ar atmosphere, and cooled to 0 °C. To this was added TEA (12 mmol), and the mixture was stirred for 10 min, at which time freshly distilled methanesulfonyl chloride (6 mmol) was added dropwise via a syringe. The resulting mixture was stirred for 1 h, and then a solution of alcohol **5** (12.0 mmol) and DMAP (1.2 mmol) in 2 mL of CH_2Cl_2 was added. This mixture was stirred for 1 h at 0 °C, brought to room temperature and stirred for 16 h. The reaction mixture was diluted with 150 mL of Et_2O and washed sequentially with 2 x 10-mL portions of 10% HCl, and 20 mL each of water, sat. $NaHCO_3$ and brine. The ethereal solution was dried ($MgSO_4$) filtered and concentrated to give a pale yellow oil, which upon chromatographic purification provided **7** (70% yield) as an inseparable 1:1 mixture of two diastereomers: *Rf* 0.44 (20% EtOAc/Skelly-B); IR 1735 (s) cm^{-1}; ^1H NMR δ (for mixture) 4.85 (m, 1H, SiOC-H), 4.78 (m, 2H, allyl CH_2), 4.50 (m, 1H, allyl CH_2), 3.35, 3.34 (2 x s, 3H total, O-CH_3), 3.31 (s, broad, 1H, C(2)-H), 2.98 (ddd, J = 4.0 Hz, 1H, C(1)-H), 2.45 (m, 1H), 2.20

(m, 2H), 1.96 (m, 1H), 1.75 (s, broad, 3H, vinyl CH_3), 1.70-1.35 (m, 6H), 0.95 (m, 4H, includes 2 x d, C(4)-CH_3), 0.86 (s, 9H, *tert*-Bu), 0.08 (m, 6H, $Si(CH_3)_2$); HRMS (CI) *m/z* calcd for $C_{22}H_{41}O_4Si$ $(M+H)^+$ 397.2761, found 397.2774.

Methyl (1*R*,2*S*,4*S*)-1-[(1*R*,3*R*)-3-(*tert*-Butyldimethylsilyl)oxy-1-methyl-2-methylenecyclopentyl]-2-methoxy-4-methylcyclohexanecarboxylate (9a) and Methyl (1*R*,2*S*,4*S*)-1-[(1*S*,3*S*)-3-(*tert*-Butyldimethylsilyl)oxy-1-methyl-2-methylenecyclopentyl]-2-methoxy-4-methylcyclohexanecarboxylate (9b).

A solution of LDA (2.2 mmol) in 4.0 mL of THF was prepared and cooled to -110 °C under an N_2 atmosphere. To this was added via cannula 3.0 mL of the supernatant centrifugate of a solution of TMSCl/TEA/THF (2.0:0.5:3.7, volume ratio) which had been precooled to -78 °C. The resulting mixture was stirred for 2 min and then a solution of **7** (1.0 mmol) in 1 mL of THF, precooled to -78 °C, was added dropwise via cannula over a period of 1 min. This mixture was maintained at -110 °C for 10 min and then gradually allowed to warm to 0 °C. The solution of crude ketene silyl acetals **8** was allowed to warm to room temperature and then heated under reflux for 12 h. The reaction mixture was diluted with 25 mL of Et_2O and stirred with 5 mL of 5% HCl for 10 min. The biphasic mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with 2 x 10-mL portions of Et_2O. The combined organic extracts were washed with 10 mL of 5% HCl solution and brine (acidified to pH 2) and dried ($MgSO_4$). The ethereal solution of the rearranged acids was concentrated to approximately 1 mL, and the concentrate was purified by chromatography on silica gel. The column fractions containing the carboxylic acids (*Rf* 0.37, 20% EtOAc/Skelly-B) were combined and concentrated to a volume of about 10 mL. This solution was treated with excess ethereal CH_2N_2 to provide a 92:8 mixture of diastereomers **9** (45% combined yield) as a colorless liquid: *Rf* 0.41 (10% Et_2O/Skelly-B); ^1H NMR (**9a**, 500 MHz) δ 5.03 (d, *J* = 1.5 Hz, 1H, exo-methylene), 4.65 (d, *J* = 2.2 Hz, 1H, exo-methylene), 4.33 (m, 1H, SiOC-H), 3.92 (broad, 1H, C(2)-H), 3.59 (s, 3H, ester CH_3), 3.23 (s, 3H, ether CH_3), 2.18-2.05 (m, 2H), 1.92-1.70 (m, 4H), 1.61 (m, 1H), 1.44 (m, 1H), 1.32 (m, 2H), 1.20 (m, 1H), 1.14 (s, 3H, quaternary CH_3), 1.08 (d, *J* = 7.4 Hz, 3H, C(4)-CH_3), 0.90 (s, 9H, *tert*-Bu), 0.09, 0.06 (2 x s, 6H, $Si(CH_3)_2$); ^{13}C NMR (**9a**) δ 174.34, 160.13, 106.31, 78.78, 58.50, 55.32, 50.79, 47.79, 32.16, 31.90, 29.44, 29.19, 27.53, 25.95, 25.79, 20.65, 20.03, 18.41, -4.72.

Methyl (1*R*,2*S*,4*S*)-1-[(1*R*,3*R*)-3-Hydroxy-1-methyl-2-methylenecyclopentyl]-2-methoxy-4-methylcyclohexanecarboxylate and Methyl (1*R*,2*S*,4*S*)-1-[(1*S*,3*S*)-3-Hydroxy-1-methyl-2-methylenecyclopentyl]-2-methoxy-4-methylcyclohexanecarboxylate.

A solution of **9** (0.17 mmol) in 10 mL of THF was treated with TBAF·H_2O (0.46 mmol) for 3 h at RT. The reaction mixture was then partitioned between 50 mL of Et_2O and 10 mL of water. The organic layer was separated, dried ($MgSO_4$) and concentrated to afford a yellow oil. The concentrate was purified by chromatography to give the alcohols (82% yield) as a 92:8 mixture of two isomers: *Rf* 0.13 (20% EtOAc/Skelly-B); ^1H NMR δ (for major diastereomer) 5.25 (d, *J* = 1.4 Hz, 1H, exo-methylene), 4.80 (d, *J* = 2.1 Hz, 1H, exo-methylene), 4.32 (m, 1H), 3.96 (broad s, 1H, C(2)-H), 3.29 (s, 3H, ester CH_3), 2.91 (s, 3H, ether CH_3),

2.22-2.14 (m, 2H), 2.05-1.70 (m, 6H), 1.48 (m, 1H), 1.39-1.00 (m, 3H), 1.25 (s, 3H, quaternary CH_3) 1.16 (d, J = 7.9 Hz, 3H, C(4)-CH_3); HRMS (CI) m/z calcd for $C_{17}H_{29}O_4$ $(M+H)^+$ 297.2065, found 297.2056.

(-)-(1*S*,3*R*,4*R*,7*S*,8*R*,11*S*)-7,11-Dimethyl-4-hydroxy-3-iodomethyl-8-methoxycarbonyl-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (11).

The alcohols (0.12 mmol) were dissolved in 1 mL of CH_3CN and cooled to 0 °C under an atmosphere of Ar. To this were sequentially added $NaHCO_3$ (0.9 mmol) and I_2 (0.23 mmol), and the resulting mixture was stirred for 3 h at 0 °C. The reaction was quenched at the same temperature by successive addition of 1 mL each of water and sat. $NaHCO_3$ followed by solid $Na_2S_2O_3$ (0.2 g). The resulting slurry was extracted with 3 x 10-mL portions of Et_2O, and the combined ethereal extracts were washed with 5 mL of water, 2 x 5-mL portions of 10% aq. $Na_2S_2O_3$, 5 mL each of water and brine and then dried ($MgSO_4$). Removal of solvents and column chromatography afforded **11** (87% yield) as a colorless viscous oil: Rf 0.35 (30% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -1.3° (c = 1.0); IR 3500 (m, broad), 1730 (s) cm^{-1}; ^1H NMR (C_6D_6) δ 4.36 (broad, s, 1H, C(1)-H), 4.10 (m, 1H, C(4)-H), 3.54 (d, J = 9.9 Hz, 1H, CH_2-I), 3.23 (s, 3H, ester CH_3), 3.17 (d, J = 9.9 Hz, 1H, CH_2-I), 2.02-1.85 (m, 2H), 1.80 (m, 5H), 1.45 (m, 1H), 1.33-1.12 (m, 4H), 1.18 (d, J = 7.3 Hz, 3H, C(11)-CH_3), 1.08 (s, 3H, C(7)-CH_3); ^{13}C NMR δ 174.04, 92.13, 81.85, 76.32, 59.14, 55.48, 51.73, 38.03, 32.13, 31.12, 28.41, 24.75, 22.39, 19.95, 19.51, 11.84; HRMS (CI) m/z calcd for $C_{16}H_{26}O_4I$ $(M+H)^+$ 409.0875, found 409.0868.

(+)-(1*S*,3*S*,7*S*,8*R*,11*S*)-7,11-Dimethyl-3-iodomethyl-8-methoxycarbonyl-4-oxo-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (12).

A dry 25-mL flask, equipped for magnetic stirring, was charged with 4 mL of CH_2Cl_2 and freshly distilled oxalyl chloride (1.7 mmol) and cooled to -78 °C under an N_2 atmosphere. A solution of DMSO (3.6 mmol) in 0.8 mL of CH_2Cl_2 was added to the reaction flask dropwise via syringe. After this mixture was stirred for 2 min, a solution of **11** (1.3 mmol) in 2.5 mL of CH_2Cl_2 was added dropwise via cannula. The resulting cloudy solution was stirred for 15 min at -78 °C, at which time 4.5 mL of TEA was added. The white slush-like mixture was stirred for an additional 15 min at the same temperature and then allowed to warm to room temperature. The reaction was quenched with 8 mL of 1% HCl, and the mixture was extracted with 3 x 40-mL portions of Et_2O. The organic layers were combined and washed successively with 2 x 15-mL portions of 1% HCl, 15 mL each of water and sat. $NaHCO_3$ and then dried (K_2CO_3). Solvent removal and chromatography afforded ketoester **12** (98% yield) as a colorless liquid after chromatography: Rf 0.31, (30% EtOAc/Skelly-B); $[\alpha]_D^{23}$ +2.2° (c = 1.6); IR 1750, 1725 (s) cm^{-1}; ^1H NMR δ 4.09 (s, broad, 1H, C(1)-H), 3.72 (s, 3H, ester CH_3), 3.43 (d, J = 10.7 Hz, 1H, CH_2-I), 3.15 (d, J = 10.7 Hz, 1H, CH_2-I), 2.50 (m, 1H), 2.35 (m, 1H), 1.86-1.50 (m, 7H), 1.49 (s, 3H), 1.41 (m, 1H), 1.30 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 214.90, 173.04, 85.43, 76.35, 59.14, 52.80, 51.83, 36.82, 30.44, 30.38, 28.22, 24.75, 21.62, 20.12, 18.06, 2.68; HRMS (CI) m/z calcd for $C_{16}H_{24}O_4I$ $(M+H)^+$ 407.0719, found 407.0711.

(-)-(1*S*,3*R*,4*S*,7*S*,8*R*,11*S*)-7,11-Dimethyl-4-hydroxy-3-iodomethyl-8-methoxycarbonyl-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (13).

A solution of **12** (0.69 mmol) in 20 mL of anhydrous MeOH was cooled to -20 °C under an Ar atmosphere. To this was added $NaBH_4$ (5.5 mmol) in one portion, and the resulting mixture was stirred at the same temperature for 2 h. At this time the reaction was carefully quenched by addition of water (5 mL) and the resulting slurry was extracted with 2 x 25-mL portions of Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated, and the crude mixture was purified by chromatography to afford **13** (99% yield) as a colorless liquid: *Rf* 0.30 (30% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -7.1° (c = 1.5); IR 3500 (m, broad), 1720 (s) cm^{-1}; ^{1}H NMR δ 4.42 (s, broad, 1H, C(1)-H), 4.01 (d, *J* = 4.3 Hz, 1H, C(4)-H), 3.68 (s, 3H, ester CH_3), 3.49 (d, *J* = 10.3 Hz, 1H, CH_2-I), 3.05 (d, *J* = 10.3 Hz, 1H, CH_2-I), 2.66 (s, 1H, OH), 2.08-1.58 (m, 7H), 1.45 (m, 1H), 1.40-1.20 (m, 3H), 1.16 (m, 6H, C(7)-CH_3, and C(11)-CH_3); ^{13}C NMR δ 173.41, 89.60, 79.83, 76.82, 57.12, 56.60, 51.62, 35.92, 31.04, 30.62, 28.32, 24.80, 21.73, 19.85, 16.42, 13.80; HRMS (CI) *m/z* calcd for $C_{16}H_{26}O_4I$ $(M+H)^+$ 409.0875, found 409.0887.

(-)-(1*S*,3*R*,4*S*,7*S*,8*R*,11*S*)-4-(*tert*-Butyldimethylsilyl)oxy-7,11-dimethyl-3-iodomethyl-8-methoxycarbonyl-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (14).

Following the procedure of Corey, *et al.*,[30] a solution of **13** (0.68 mmol) in 5 mL of CH_2Cl_2, at 0 °C, was treated with TBDMSOTf (0.87 mmol) in the presence of 2,6-lutidine (1.8 mmol). The reaction mixture was allowed to warm to RT, stirred at this temperature for 3 h, and then quenched by being poured into a mixture of 50 mL of Et_2O and 10 mL of water. The layers were separated and the organic layer was washed with 10 mL of sat. NaCl and dried ($MgSO_4$). Solvent removal followed by chromatography provided **14** (99% yield) as a clear colorless liquid: *Rf* 0.63 (30% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -9.8° (c = 1.5); IR 1720 cm^{-1}; ^{1}H NMR δ 4.62 (m, 1H, C(1)-H), 4.10 (m, 1H, C(4)-H), 3.68 (s, 3H, ester CH_3), 3.39 (d, *J* = 10.3 Hz, 1H, CH_2-I), 3.00 (d, *J* = 10.3 Hz, 1H, CH_2-I), 2.00 (m, 1H), 1.92-1.35 (m, 8H), 1.32 (m, 2H), 1.15 (m, 6H, C(7)-CH_3 and C(11)-CH_3), 0.89 (s, 9H, *tert*-Bu), 0.19 (s, 3H, Si-CH_3), 0.10 (s, 3H, Si-CH_3); ^{13}C NMR δ 174.16, 88.57, 80.77, 75.66, 57.19, 56.15, 51.37, 35.84, 32.90, 30.47, 28.69, 25.78, 25.68, 25.04, 21.83, 20.12, 17.99, 17.01, 13.78, -2.94, -4.62; HRMS (CI) *m/z* calcd for $C_{22}H_{40}O_4SiI$ $(M+H)^+$ 523.1740, found 523.1726.

(-)-(1*S*,3*R*,4*S*,7*S*,8*S*,11*S*)-4-(*tert*-Butyldimethylsilyl)oxy-7,11-dimethyl-8-hydroxymethyl-3-iodomethyl-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (15).

Ester **14** (0.7 mmol) was dissolved in toluene (8 mL) in a 25-mL flask, and the solution was cooled to 0 °C under an inert atmosphere. To this was added DIBAL-H (2.0 mL, 1.0 *M* in toluene) dropwise over a period of 5 min, and the resulting mixture was stirred at 0 °C for 5 h. The reaction was quenched by carefully adding 7 mL of a saturated solution of sodium potassium tartrate, and the resulting mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was extracted with 2 x 8-mL portions of Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed to provide the hydroxymethyl compound **15** (83 % yield) as a viscous liquid: *Rf* 0.36 (30% EtOAc/Skelly-B);

$[\alpha]_D^{23}$ -12.4° (c = 2.0); IR 3350 (m, broad) cm^{-1}; ^1H NMR δ 4.06 (m, 1H, C4-H), 3.75 (m, 2H, C(1)-H, and 1H of CH_2-O), 3.62 (m, 1H, CH_2-O), 3.46 (d, *J* = 10.3 Hz, 1H, CH_2-I), 3.00 (d, *J* = 10.3 Hz, 1H, CH_2-I), 2.25 (m 1H), 1.85 (m, 2H), 1.72-1.35 (m, 8H), 1.17 (d, *J* = 7.3 Hz, 3H, C(11)-CH_3), 1.08 (s, 3H, C(7)-CH_3), 0.86 (s, 9H, *tert*-Bu), 0.18 (s, 3H, Si-CH_3), 0.11 (s, 3H, Si-CH_3); ^{13}C NMR δ 88.44, 80.88, 62.26, 57.20, 48.34, 34.53, 33.10, 30.91, 26.93, 25.79, 25.40, 20.68, 19.16, 18.77, 17.96, 14.92, -3.76, -4.63; HRMS (CI) *m/z* calcd for $C_{21}H_{40}O_3SiI$ $(M+H)^+$ 495.1791, found 495.1782.

(-)-(1*S*,3*R*,4*S*,7*S*,8*S*,11*S*)-4-(*tert*-Butyldimethylsilyl)oxy-8-[(*tert*-butyldimethylsilyl)oxy] methyl-7,11-dimethyl-3-iodomethyl-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (16).

Silylation of **15** (0.39 mmol) with TBDMSOTf according to the protocol used for **14** gave **16** (99% yield) as a colorless liquid after chromatography: *Rf* 0.38 (Skelly-B); $[\alpha]_D^{23}$ -10.5° (c = 1.0); ^1H NMR (500 MHz) δ 4.03 (m, 1H, C(4)-H), 3.70 (m, 1H, C(1)-H), 3.61 (d, *J* = 10.3 Hz, 1H, CH_2-O-Si), 3.48 (d, *J* = 10.3 Hz, 1H, CH_2-O-Si), 3.45 (d, *J* = 10.3 Hz, 1H, CH_2-I), 2.98 (d, *J* = 10.3 Hz, 1H, CH_2-I), 2.21 (m, 1H), 1.81 (m, 2H), 1.65-1.48 (m, 4H), 1.32-1.55 (m, 4H), 1.15 (d, *J* = 7.3 Hz, 3H, C(11)-CH_3), 1.04 (s, 3H, C(7)-CH_3), 0.86 (s, 9H, *tert*-Bu), 0.85 (s, 9H, *tert*-Bu), 0.16 (s, 3H, Si-CH_3), 0.09 (s, 3H, Si-CH_3), 0.01 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 88.34, 81.03, 76.54, 62.07, 57.45, 48.26, 34.41, 33.02, 31.06, 27.01, 25.86, 25.49, 20.76, 19.31, 18.40, 18.18, 18.02, 15.40, -3.72, -4.56, -5.62, -5.72; HRMS (CI) *m/z* calcd for $C_{27}H_{54}O_3Si_2I$ $(M+H)^+$ 609.2656, found 609.2659.

(-)-(2*S*,5*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]methyl-2-[(1*R*,3*S*)-3-(*tert*-butyldimethylsilyl)-oxy-1-methyl-2-methylenecyclopentyl]-5-methylcyclohexanone (18).

A mixture of **16** (0.38 mmol), purified Zn dust (3.0 mmol) and pyridine (2 mL) in 4:1 mixture (v/v) of THF:95% EtOH (10 mL) was heated under reflux for 20 h in an atmosphere of N_2. The reaction mixture was cooled and filtered through a short pad of activated basic alumina. The filter cake was washed with 40 mL of EtOAc, and the washings were combined with filtrate. Alcohol **17** (0.19 g) was obtained as a viscous oil upon concentration of the filtrate and was immediately oxidized according to the procedure used with **11** to give ketone **18** (70% yield from **16**) as a colorless liquid after chromatography: *Rf* 0.48 (5% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -32.9° (c = 1.0); IR 1680 (s) cm^{-1}; ^1H NMR δ 5.16, 5.02 (2 x s, 2 x 1H, exo-methylene), 4.31 (m, 1H, SiO-CH), 4.07, 3.64 (2 x d, *J* = 9.5 Hz, 2 x 1H, SiO-CH_2), 2.45 (m, 1H), 2.23-1.96 (m, 4H), 1.85 (m, 2H), 1.62-1.38 (m, 4H), 1.18 (s, 3H, quaternary CH_3), 0.95 (d, *J* = 6.5 Hz, 3H, C(5)-CH_3), 0.87 (s, 9H, *tert*-Bu), 0.85 (s, 9H, *tert*-Bu), 0.06 (2 x s, 6H, $Si(CH_3)_2$), 0.03 (2 x s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 213.87, 160.79, 112.62, 78.20, 66.04, 56.59, 50.06, 49.63, 36.55, 32.72, 30.16, 30.07, 27.86, 26.83, 25.83, 21.36, 18.06, -4.51, -4.64, -5.58, -5.64; HRMS (CI) *m/z* calcd for $C_{27}H_{53}O_3Si_2$ $(M+H)^+$ 481.3533, found 481.3523.

(-)-(2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]methyl-2-[(1*R*,3*S*)-3-(*tert*-butyldimethylsilyl)oxy-1-methyl-2-methylenecyclopentyl]-5-methyl-5-cyclohexen-1-one (19).

A procedure modeled after that of Reich, *et al.*,[21] was used. A solution of LDA (1.0 mmol) in 5 mL of THF was cooled to -78 °C, and a solution of **18** (0.26 mmol) in 1 mL THF was added dropwise. The resulting mixture was stirred for 15 min, at which time a solution of PhSeBr (0.75 mmol) in 1 mL of THF was rapidly added. After 3 min the reaction was quenched by adding 5 mL of 1% HCl at -78 °C. The resulting mixture was then allowed to warm to RT, transferred to a separatory funnel containing 50 mL of Et_2O and 10 mL of water, and the organic layer was separated. The aqueous layer was extracted once with 25 mL of Et_2O, and the combined organic layers were dried (K_2CO_3) and concentrated to afford the crude selenide as a yellow liquid. This was dissolved in 10 mL of CH_2Cl_2 and treated with 5 mL of a 1:1 mixture of 30% H_2O_2 and water in the presence of a small amount of pyridine for 45 min. At the end of this time the organic layer was separated and the aqueous layer was extracted with 2 x 25-mL portions of CH_2Cl_2. The combined organic extracts were dried (K_2CO_3), concentrated, and the residue was purified by chromatography to give **19** (85% yield) as a colorless oil: R_f 0.21 (5% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -24.2° (c = 2.0); IR 1650 (s) cm^{-1}; ^1H NMR δ 5.81 (s, broad, 1H, C(6)-H), 5.20, 5.15 (2 x s, 2 x 1H, exo-methylene), 4.31 (m, 1H, SiOC-H), 4.10, 3.75 (2 x d, J = 9.6 Hz, 1H, SiO-CH_2), 2.45 (m, 1H), 2.26-1.93 (m, 3H), 1.87 (s, 3H, C(5)-CH_3), 1.65-1.38 (m, 4H), 1.26 (s, 3H, quaternary CH_3), 0.86 (s, 9H, *tert*-Bu), 0.83 (s, 9H, *tert*-Bu), 0.05 (2 x s, 6H, Si$(CH_3)_2$), 0.01, -0.01 (2 x s, 2 x 3H, Si$(CH_3)_2$); ^{13}C NMR δ 202.70, 160.71, 160.26, 128.53, 112.80, 78.22, 67.29, 52.34, 49.93, 36.56, 32.62, 29.58, 28.46, 26.85, 25.85, 25.79, 24.07, 18.19, 18.05, -4.45, -4.64, -5.55, -5.63; HRMS (CI) *m/z* calcd for $C_{27}H_{51}O_3Si_2$ $(M+H)^+$ 479.3376, found 479.3384.

(-)-(1*S*,2*S*)-2-Acetoxy-1-[(*tert*-butyldimethylsilyl)oxy]methyl-1-[(1*R*,3*S*)-3-(*tert*-butyldimethylsilyl)oxy-1-methyl-2-methylenecyclopentyl]-4-methyl-3-cyclohexene (20) and (-)-(1*S*,2*S*)-2-Acetoxy-1-[(*tert*-butyldimethylsilyl)oxy]methyl-1-[(1*R*,3*S*)-3-acetoxy-1-methyl-2-methylenecyclopentyl]-4-methyl-3-cyclohexene (21)

Reduction of enone **19** (0.21 mmol) with DIBAL-H according to the protocol used with **14** afforded crude alcohol, which was immediately dissolved in 1.0 mL of pyridine and treated with 0.5 mL of acetic anhydride. This mixture was stirred for 48 h at room temperature under an Ar atmosphere, diluted with 50 mL of Et_2O, sequentially washed with 2 x 10-mL portions of sat. $CuSO_4$, 10 mL each of water, and brine and dried ($MgSO_4$). Solvent removal gave a yellow oil which was chromatographed to provide monoacetate **20** (35% yield) and diacetate **21** (31% yield) as colorless oils.

Data for **20**: R_f 0.5 (10% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -14.5° (c = 1.0); ^1H NMR δ 5.65 (m, 1H, C(3)-H), 5.42 (d, J = 5.4 Hz, 1H, C(2)-H), 5.27, 5.19 (2 x s, 2H, exo-methylene), 4.31 (m, 1H, SiOC-H), 3.78, 3.55 (2 x d, J = 10.9 Hz, 2 x 1H, SiO-CH_2), 2.65 (m, 1H), 2.03 (s, 3H, acetoxy CH_3), 2.08-1.75 (m, 3H), 1.67 (s, 3H, C(4)-CH_3), 1.70-1.52 (m, 3H), 1.25 (m, 1H), 1.21 (s, 3H, quaternary CH_3), 0.89, 0.87 (2 x s, 2 x 9H, 2 x *tert*-Bu), 0.07, 0.06 (2 x s, 6H, Si$(CH_3)_2$), 0.00 (2 x s, 6H, Si$(CH_3)_2$); ^{13}C NMR δ 170.26, 161.49, 138.91, 120.34, 112.96, 78.17, 70.27, 65.22, 50.18, 42.32, 36.91, 33.49, 28.22, 28.19, 25.84, 23.04,

22.94, 21.87, 18.42, 18.26, -4.61, -4.78, -5.69; HRMS (CI) *m/z* calcd for $C_{29}H_{55}O_4Si_2$ $(M+H)^+$ 523.3638, found 523.3624.

Data for **21**: *Rf* 0.22 (10% EtOAc/Skelly-B); $[\alpha]_D^{23}$ -18.3° (c = 1.0); ^1H NMR δ 5.72 (m, 1H, C(3)-H), 5.55 (s, 1H, exo-methylene), 5.42 (m, 2H, C(2)-H and exo-methylene), 3.75, 3.56 (2 x d, *J* = 10.2 Hz, 2 x 1H, SiO-CH_2), 2.62 (m, 1H), 2.04 (s, 6H, 2 x CH_3, acetoxy), 2.16-1.75 (m, 6H), 1.73-1.60 (m, 2H), 1.66 (s, 3H, C(4)-CH_3), 1.32 (m, 2H), 1.25 (s, 3H, quaternary CH_3), 0.86 (s, 9H, *tert*-Bu), -0.02 (2 x s, 6H, Si $(CH_3)_2$); ^{13}C NMR (125 MHz) δ 170.55, 170.32, 156.87, 138.65, 120.28, 117.41, 79.94, 70.09, 64.98, 50.58, 42.90, 36.97, 30.26, 28.22, 25.82, 22.90, 22.72, 21.85, 21.56, 18.10, -5.72; HRMS (CI) *m/z* calcd for $C_{25}H_{43}O_5Si$ $(M+H)^+$ 451.2879, found 451.2864.

(+)-15-Hydroxytrichothec-9,12-diene (3).

A dry 4-mL polypropylene vial was charged with acetate **20** (0.03 mmol) and 2 mL of dry CH_3CN, the resulting solution was cooled to 0 °C under an Ar atmosphere, and HF·pyridine complex (0.4 mL) was added; this mixture was maintained at 0 °C for 0.5 h. The solution was allowed to warm to RT and stirred at that temperature for 2 h, after which it was transferred to a separatory funnel containing 50 mL of Et_2O and 10 mL of sat. $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with an additional 10 mL of Et_2O. The organic extracts were combined, washed with 10 mL of sat. $NaHCO_3$ and dried (K_2CO_3). Solvent was removed and the residue was purified by chromatography to afford **3** (85% yield) as a colorless oil: *Rf* 0.29 (30% EtOAc/Skelly-B); $[\alpha]_D^{23}$ +33.1° (c = 0.5); IR (CCl_4) 3620 (m) cm^{-1}; ^1H NMR (500 MHz) δ 5.39 (m, 1H, C(10)-H), 4.94, 4.59 (2 x s, 2 x 1H, C(13)-H_2), 4.27 (d, *J* = 4.9 Hz, 1H, C(2)-H), 3.70 (dd, *J* = 11.8, 4.3 Hz, 1H, CH_2-O), 3.68 (d, *J* = 5.4 Hz, 1H, C(11)-H), 3.46 (dd, *J* = 11.1, 4.0 Hz, 1H, CH_2-O), 2.27 (ddd, *J* = 13.7, 9.3, 4.7 Hz, 1H, C(4)-H), 2.05 (m, 2H), 1.88-1.72 (m, 4H), 1.67 (s, 3H, C(9)-CH_3), 1.60 (m, 1H), 1.39 (ddd, *J* = 13.0, 12.9, 5.1 Hz, 1H, C(4)-H), 1.15 (s, 3H, C(5)-CH_3); ^{13}C NMR (125 MHz) δ 155.30 (C-12), 140.51 (C-9), 119.70 (C-10), 102.95 (C-13), 79.83 (C-2), 66.83 (C-11), 63.11 (C-15), 47.74 (C-6), 44.12 (C-5), 32.66 (C-4), 28.67 (C-8), 27.32 (C-3), 23.35 (C-16), 19.90 (C-7), 17.80 (C-14); HRMS (CI) *m/z* calcd for $C_{15}H_{23}O_2$ $(M+H)^+$ 235.1698, found 235.1707.

REFERENCES AND FOOTNOTES

1. Taken in part from the Ph.D. dissertation of R. D. Selliah, The University of Texas at Austin, 1992.
2. (a) Joffe, A. Z. *Fusarium Species: Their Biology and Toxicology*, John Wiley, New York, 1986. (b) Ueno, Y. *Trichothecenes-Chemical, Biological and Toxicological Aspects, Developments in Food Science. 4*; Elsevier: New York, 1983, Chapters 1, 5, 6.
3. ApSimon, J. W.; Blackwell, B. A.; Blais, C.; Fielder, D. A.; Greenhalgh, R.; Kasitu, G.; Miller, J. D.; Savard, M. *Pure Appl. Chem.* **1990**, *62*, 1339–1346, and references therein cited.
4. *Mycotoxic Fungi, Mycotoxins and Mycotoxicoses*; Wyllie, T. D.; Morehouse, L. G., Eds.; Marcell Dekker: New York, 1978; Vol. 2.
5. (a) Härri, E.; Loeffler, W.; Sigg, H. P.; Stahelin, H.; Stoll, Ch.; Tamm, Ch.; Wiesinger, D. *Helv. Chim. Acta*, **1962**, *45*, 839–853. (b) Kaneko, T.; Schmitz, H.; Essery, J. M.; Rose, W.; Howel, H. G.:

O'Herron, F. A.; Nachfolger, S.; Huftlaen, J.; Bradner, W. T.; Partyka, R. A.; Doyle, T. W.; Davies, J.; Cundliffe, E. *J. Med. Chem.* **1982**, *25*, 579–589; (c) Doyle, T. W.; Bradner, W. T. In *Anticancer Agents Based on Natural Products*; Cassady, J. M.; Douros, J. D., Eds.; Academic: New York, 1980; Vol. 6, p 43.

6. (a) Yap, A. -Y.; Murphy, W. K.; DiStefano, A.; Blumenschein, G. R.; Bodey, G. P. *Cancer Treat. Report*, **1979**, *63*, 789–791. (b) Adler, S. S.; Lowenbraun, S.; Birch, B.; Jarrel, R.; Garrard, J. *Cancer Treat. Report*, **1984**, *68*, 423–425.
7. Conner, M. W.; Camargo, J. D.; Punyarit, P.; Riengropitak, S.; Rogers, A. E.; Newberne, P. M. *Fundam. Appl. Toxicol.* **1986**, *7*, 153–164.
8. O'Brien, M. K.; Pearson, A. J.; Pinkerton, A. A.; Schmidt, W.; Willman, K. *J. Am. Chem. Soc.* **1989**, *111*, 1499–1501, and references therein cited.
9. (a) Brooks, D. W.; Grothaus, P. G.; Mazdiyansi, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472–4473; (b) Hua, D. H.; Venkataraman, S.; Chan; Y.-K. R.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741–4748.
10. Gilbert, J. C.; Selliah, R. D. *Tetrahedron Lett.* **1992**, *33*, 6259–6262.
11. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279–3285. (c) Pereira, S.; Srebnik, M. *Aldrichchim. Acta* **1993**, *26*, 17–29, and references cited therein.
12. Ziegler, F. E.; Nagia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987–3991.
13. The alcohol **5** is reported to decompose within two days, even when kept at -20 ^{o}C.[12] We have found that quenching the reaction mixture with 20% aqueous sodium dihydrogen phosphate rather than saturated ammonium chloride provides **5** that is stable at ambient temperatures for several days. The source of this difference in stabilities of the product is unknown.
14. (a) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* in press; (b) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1986**, *51*, 4485–4488.
15. For a review of the different approaches to the construction of the trichothecene skeleton see: McDougal, P. G.; Schmuff, N. R. in *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, Ch. eds.; Springer-Verlag: New York, 1985; Vol. 47, p 153.
16. Chandrasekaren, S.; Turner, J. V. *Synth. Commun.* **1982**, *12*, 727–731.
17. Gilbert, J. C.; Wiechman, B. E. *J. Org. Chem.* **1986**, *51*, 258–260.
18. Mancuso, A. J.; Swern, D. *Synthesis*, **1981**, 165–185.
19. Interestingly, reduction with DIBAL-H of an analog of **12** in which the ester function has been converted to an alcohol and protected as a TBDMS ether produces **11** (R^1 = $CH_2OTBDMS$, R^2 = OH. This result presumably reflects complexation of the reducing agent with the oxygen of the iodomethyl ether function and subsequent delivery of hydride from the endo (concave) face of the molecule.
20. For the use of pyridine to complex Zn^{+2} see, for example, Denis, J. M.; Girad, C.; Conia, J. M. *Synthesis*, **1972**, 549–551.
21. Reich, H. J.; Renga, J. M.; Reich, I. C. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

22. Evidence for the desilylation as occurring at C-2 rather than C-15 was inferred from results obtained from similar reduction/acetylation reactions carried out in the trichodiene series[23] wherein a compound similar to **19**, except that it lacked the C-2 hydroxy group, did not show desilylation of the C-15 silyl ether unit.
23. Selliah, R. C. Ph. D. Dissertation, The University of Texas at Austin, 1992.
24. Greenhalgh, R.; Blackwell, B. A.; Savard, M. E. *Tetrahedron*, **1989**, *45*, 2373–2383.
25. The epoxidation of the 12,13-olefin in compounds similar to **3** to provide trichothecenes is documented.[15]
26. Djerassi, C.; Burakevich, J.; Chamberlin, J. W.; Elad, D.; Toda, T.; Stork, G. *J. Am. Chem. Soc.* **1964**, *84*, 465–471.
27. Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
28. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: New York, 1980.
29. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509–510.
30. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

Acknowledgments: Financial support of this research by the Robert A. Welch Foundation (Grant F-815) is gratefully acknowledged.

(*Received in USA* 3 *September* 1993; *accepted* 22 *October* 1993)